CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206276Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 206276
Related IND	IND 60991
Applicant Name	Alcon Research Ltd.
Date of Submission **Date of Receipt**	July 30, 2014 July 30, 2014
Review Type	Priority (includes pediatric data)
PDUFA Goal Date	January 30, 2015
Proprietary Name / **Established (USAN) Name**	PAZEO Olopatadine hydrochloride ophthalmic solution, 0.7%
Drug Class **Formulation** **Presentation** **Use**	Relatively selective histamine H1 antagonist, inhibitor of histamine release from mast cells Ophthalmic solution • 2.5 mL fill volume in 4 mL bottle One drop in each affected eye once daily
Proposed Indication	Treatment of ocular itching associated with allergic conjunctivitis
Action for Application	*Approval*

Material Reviewed/Consulted OAP Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Wiley Chambers 9/15/2014, 12/14/2014
CDTL Review	Bill Boyd 1/29/2015
Statistical Review	Yunfan Deng, Yan Wang 1/2/2015
Pharmacology/Toxicology Review	Aaron Ruhland, Lori Kotch 12/31/2014
Clinical Pharmacology Review	Gerlie Gieser, Philip Colangelo 10/16/2014
OPQ	Libaniel Rodriguez, Balajee Shanmugam, Rapti Madurawe 12/22/2014
Quality Microbiology Review	Stephen Langille, Bryan Riley 1/5/2015
Biopharmaceutics Review, OPQ	Banu Zolnik, Elsbeth Chikhale 12/23/2014
OC/Facilities Inspection	Acceptable (CMC review)
OSI/DGCPC	Roy Blay 12/11/2014, 1/7/2015
OSE/DMEPA Proprietary Name Letter	Rachna Kapoor 12/9/2014 Karen Townsend 12/10/2014
OSE/DMEPA Labeling Review	Rachna Kapoor, Yelena Maslov 11/19/2014
OPDP/DPDP (formerly DDMAC)	Christine Corser 1/6/2015
Pediatric Review Committee	George Greeley 12/05/2014
Pediatric Exclusivity	Matt Bacho 12/16/2014
Project Manager	Lois Almoza

OND=Office of New Drugs,
CDTL=Cross-Discipline Team Leader
OPQ = Office of Product Quality
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

Table of Contents:

1. Summary and Recommendations

Pazeo (olopatadine hydrochloride ophthalmic solution) 0.7% is a histamine (H1) receptor antagonist that inhibits the mast cells from releasing histamine. It is proposed for the treatment of ocular itching associated with allergic conjunctivitis.

The Indications and Usage section, and the Dosage and Administration section of labeling will provide the following information:

> **1 INDICATIONS AND USAGE**
> PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7% is indicated for the treatment of ocular itching associated with allergic conjunctivitis.
>
> **2 DOSAGE AND ADMINISTRATION**
> The recommended dosage of PAZEO is to instill one drop in each affected eye once a day.

All disciplines recommend approval. Product labeling, including carton and container labels have been finalized. The proprietary name PAZEO was found acceptable by DMEPA. OSI recommended that data are reliable. The Office of Compliance recommended the manufacturing facilities are acceptable.

1.1 Deficiencies
None, the application will be approved.

1.2 Post-Marketing Studies:
None

1.3 Other Issues
None

2. Background

Allergic conjunctivitis is a reaction to various antigens and is characterized by itching and redness of the eye.

There are currently various products approved for use in allergic conjunctivitis. Some are labeled for ocular itching only. Others are labeled for allergic conjunctivitis, because the clinical studies demonstrated efficacy in both reducing ocular itching and ocular redness (conjunctivitis).

Lastacaft	Alcaftadine (#)	Ocular itching
Optivar	Azelastine Hydrochloride (#)	Ocular itching
Bepreve	Bepotastine (#)	Ocular itching
Elestat	Epinastine Hydrochloride (#)	Ocular itching
Alocril	Nedocromil sodium (*)	Ocular itching

Pataday	Olopatadine hydrochloride (*#)	Ocular itching
Alamast	Pemirolast potassium (*)	Ocular itching
Acular	Ketorolac tromethamine (##)	Ocular itching
Emadine	Emedastine difumarate (#)	Allergic conjunctivitis
Alrex	Loteprednol etabonate (**)	Allergic conjunctivitis
Patanol	Olopatadine hydrochloride (*#)	Allergic conjunctivitis

Source: Medical Officer Review p.4 (modified)
(#) H1 histamine receptor antagonist
(*) Mast cell stabilizer
(##) NSAID
(**) Corticosteroid

Olopatadine is approved under three Alcon NDAs:

- PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is indicated for the treatment of the signs and symptoms of allergic conjunctivitis. It is dosed as one drop in each affected eye two times per day at an interval of 6 to 8 hours. The NDA 20-688 was approved December 18, 1996. The IND is IND 44216.
- PATADAY (olopatadine hydrochloride ophthalmic solution) 0.2%, is indicated for the treatment of ocular itching associated with allergic conjunctivitis. It is dosed as one drop in each affected eye once a day. The NDA 21-545 was approved December 22, 2004. The IND is IND 60991.
- PATANASE (olopatadine hydrochloride) Nasal Spray 0.6% is indicated for the relief of the symptoms of seasonal allergic rhinitis. NDA 21-861 was approved April 15, 2008.

2.1 NDA Submission

The drug was studied under IND 60,991. Two pre-NDA meetings were held with the Division.

During the July 30, 2012, pre-NDA meeting, topics of discussion included: need for new NDA of the new formulation, need for two studies to claim superiority, need for clinical data and not modeling to support an application; adequacy of PK study, six-week safety study in 300 subjects > 2 years old, defer comments on labeling, no anticipated need for additional nonclinical studies, need for ocular distribution study, additional stability data, comparison of current and previous formulations, additional CMC information.

During the August 26, 2013, pre-NDA meeting, topics of discussion included: the clinical studies, primary endpoints, content and format of the application, statistical analysis plan, labeling, datasets, the pediatric written request, cross-referencing other approved olopatadine products in the NDA, and possible trade names; statistical comments for study C-12-053 were included in the meeting minutes.

2.2 Priority Review

The application contains results from pediatric studies and is therefore given a priority review.

3. CMC/Product Quality Microbiology

See complete CMC review, Microbiology Sterility review and Biopharmaceutics review.

3.1 Product Quality

The reviewers conclude the NDA provides adequate information to assure the identity, strength, purity, and quality of the drug product. All CMC issues have been resolved satisfactorily and there are no outstanding issues. The Office of Compliance has given an acceptable recommendation for both the drug substance manufacturing facility (b) (4) and the drug product manufacturing facility (Alcon Research, LTD., Fort Worth, Texas and Alcon-Covreour nv, Puurs, Belgium).

Olopatadine hydrochloride ophthalmic solution, 0.7% solution contains: Active: 7.76 mg olopatadine hydrochloride equivalent to 7 mg olopatadine. Inactives: povidone; hydroxypropyl-gamma-cyclodextrin; polyethylene glycol 400; hydroxypropyl methylcellulose; boric acid; mannitol; benzalkonium chloride 0.015% (preservative); hydrochloric acid/sodium hydroxide (to adjust pH); and purified water.

The product is supplied in a low density polyethylene (LDPE) white oval bottle with LDPE dispensing plug and polypropylene (PP) closure. This container/closure system is the same as use for PATANOL and PATADAY by Alcon. The product has a 2.5 mL fill trade size in a 4 mL bottle. A 0.5 mL fill size is planned as a professional sample size.

The shelf life is 104 weeks (24 months) and it is supported by the updated 78 weeks of stability data provided.

3.2 Product Quality Microbiology

The drug product will be (b) (4) filled into 4 ml LDPE dropper bottles. (b) (4)

The applicant provided a satisfactory summary of the container closure integrity (b) (4) effectiveness test methods and results, description of the manufacturing process and process controls, information on the (b) (4) operation at both drug product manufacturing facilities and the component sterilization facilities, summary of the drug product specifications, test methods and acceptance criteria; and summary of the stability protocol and stability data. The reviewer concluded the applicant has presented adequate information to mitigate risks outlined in the initial product quality microbiology risk assessment.

3.3 Biopharmaceutics – BA/BE Waiver

The Biopharmaceutics review notes that the applicant requested a waiver per 21 CFR 320.22(b)(1), however, the applicant conducted a PK study thus a waiver request is not applicable (see Section 5. Clinical Pharmacology).

3.4 USP nomenclature

The USP Nomenclature Monograph, <1121>, states that product strength is linked to the active moiety. The concentration of olopatadine hydrochloride is 0.77% in the formulation. The concentration of olopatadine in the formulation is 0.7%. After internal discussion, CMC confirmed the name and concentration should be: PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7%.

Comment:
The OPQ CMC reviewers recommend approval of the application from their perspective.

4. Nonclinical Pharmacology/Toxicology

See Pharmacology/Toxicology reviews.

The reviewer notes that Alcon conducted pharmacology, comparative ocular distribution/pharmacokinetic and ocular toxicity studies of olopatadine hydrochloride ophthalmic solution, 0.7% to support the new formulation and higher concentration of olopatadine hydrochloride compared to the previously approved formulations. The studies showed:

- A dose dependent increase in conjunctival and intraocular distribution for olopatadine hydrochloride, 0.7% compared to PATADAY®
- In pigmented rabbits, no adverse or toxic effects were attributed to olopatadine, 0.7% when administered up to four times daily for 3 months. This dose correlates with an approximate 4-fold margin over the proposed clinical dose.

All excipients are qualified for topical ophthalmic administration except hydroxypropyl-γ-cyclodextrin and povidone (b) (4) The applicant conducted a 3-month ocular toxicology study with the to-be-marketed formulation which qualifies the excipients at the proposed levels for topical ophthalmic administration.

For this submission, the applicant conducted one preclinical efficacy pharmacology study, which compared efficacy of PATADAY (olopatadine hydrochloride ophthalmic solution) 0.2% with that of olopatadine hydrochloride, 0.7% in a preclinical model of histamine-induced vascular permeability. Study results indicated that olopatadine hydrochloride, 0.7% significantly suppresses allergic conjunctival symptoms compared to PATADSY and vehicle control.

Comment: The Pharmacology/Toxicology (P/T) reviewers recommend approval. The labeling recommendations were incorporated; the Risk Summary section was streamlined so as not to be redundant with the complete summary of studies in the Animal Data section.

5. Clinical Pharmacology/Biopharmaceutics

See Clinical Pharmacology review.

The reviewer notes that the sponsor conducted PK Study C-11-036 to determine the plasma exposures to olopatadine and its two (N-oxide and mono-desmethyl) metabolites following single and repeated topical ocular administration of the proposed commercial ophthalmic solution in 24 healthy adult subjects; 19 subjects had a complete set of PK profiles on Days 1 and 7. No apparent accumulation of olopatadine was observed following repeated topical ocular administration of the proposed product for 7 days.

The mean steady state plasma olopatadine C_{max} and AUC_{0-12} measured with PAZEO in this PK study were lower (by 90% to 93%, and by 85% to 88%, respectively) than that reported in adult healthy subjects and seasonal allergic rhinitis patients following administration of PATANASE (olopatadine hydrochloride 0.6%; Alcon) Nasal Spray given 2 sprays per nostril twice daily for 14 days. The N-oxide metabolite of olopatadine (M3) was detected in less than 10% of the total plasma samples in approximately half of the study participants; the maximum plasma concentration was 0.174 ng/mL measured during the first 4 hours post-dosing. Plasma concentrations of desmethyl olopatadine (M1) were below the LLOQ (0.05 ng/mL) of the PK assay.

In healthy subjects, topical ocular dosing of 1 drop of PAZEO once daily for 7 days into both eyes resulted in mean ± SD (range) steady state plasma olopatadine C_{max} and AUC_{0-12} of 1.6 ± 0.9 ng/mL (0.6 to 4.5 ng/mL) and 9.7 ± 4.4 ng*h/mL (3.7 to 21.2 ng*h/mL), respectively. The olopatadine C_{max} and AUC_{0-12} after the first dose were similar to those measured on day 7 in these subjects, suggesting that there was no systemic accumulation of olopatadine after repeated topical ocular dosing with PAZEO. The median (range) time to achieve peak olopatadine concentrations (T_{max}) was 2.0 hours (0.25 to 4 hours). The mean ± SD (range) elimination half-life of olopatadine was 3.4 ± 1.2 hours (2 to 8 hours). N-oxide olopatadine (M3) was detected during the first 4 hours after bilateral topical ocular dosing of PAZEO in approximately half of the subjects and in less than 10% of the total plasma samples collected, at concentrations not exceeding 0.121 ng/mL on day 1 and 0.174 ng/mL on day 7. None of the plasma samples from these subjects had mono-desmethyl olopatadine (M1) concentrations that were above the lower limit of quantitation (0.05 ng/mL) of the PK assay.

Comment: The reviewers recommend approval from the Clinical Pharmacology perspective; labeling revisions have been incorporated in labeling.

6. Clinical Microbiology/Immunology

Not Applicable

7. Clinical/Statistical-Efficacy

See clinical reviews and biostatistics reviews.

The following table summarizes the features of the three Phase 3 studies submitted in support of the application. These included two conjunctival antigen challenge (CAC) studies to support the efficacy of the product and one Phase 3 safety study to provide six weeks of adverse reaction data.

Study Number	Design	Ages	Arms	Number of Subjec	Dosing	Duration
C-10-126 Phase 3 Efficacy CAC	Randomized, double masked, parallel-group, active and vehicle controlled study	18 years of age or older	Olopatadine HCl, 0.7% Olopatadine, 0.2% Vehicle	66 68 68	1 drop per eye	3 non-consecutive doses over 3 weeks
C-12-053 Phase 3 Efficacy CAC	Randomized, double masked, parallel-group, active and vehicle controlled study	18 years of age or older	Olopatadine HCl, 0.7% Olopatadine HCl, 0.2% Olopatadine HCl, 0.1% Vehicle	98 99 99 49	1 drop per eye	2 non-consecutive doses over 2 weeks
C-12-028 Phase 3 Safety	Randomized, double masked, parallel-group, vehicle controlled study	2 years of age or older	Olopatadine HCl, 0.7% Vehicle	330 169	1 drop per eye once daily	6 weeks

Clinical studies (C-10-126, C-12-028 and C-12-053) used the same, final formulation for PAZEO (FID (b) (4) and its Vehicle (FID (b) (4) Two studies (C-10-126 and C-12-053) had PATADAY as an active comparator and used the same, marketed formulation for PATADAY (FID (b) (4)
Source: adapted from Medical Officer Review

The CAC efficacy studies, C-10-126 and C-12-053, were multicenter, randomized, double-masked, vehicle controlled, parallel-group studies and used the CAC model. Then Medical Officer notes that the CAC design has been used to support the majority of drug products approved for the treatment of ocular itching. The details of the study procedure are included in the clinical review. In brief, patients with an allergic history were conjunctively challenged in both eyes with progressively higher doses of antigen until they demonstrated a ≥2+ itching and redness reaction. These patients returned for a second visit in which the dose which elicited a ≥2+ reaction was administered and only patients who demonstrated a reproducible ≥2+ reaction continued in the study. Patients returned for a third visit, during which the test drug product was administered to both eyes and after 24 hours, the antigen which reproducibly elicited a ≥2+ reaction was again administered. The patient's itching reactions were recorded at 3, 5 and 7 minutes after antigen administration, the patient's redness reactions were recorded 7, 15 and 20 minutes after antigen administration. The patient's fourth visit was a repeat of the third visit except that the time after test product administration was reduced to 16 hours. The patient's fifth visit was a repeat of the third visit, except that the time after test product administration was reduced to 27 minutes.

The study designs were similar for both studies with the exception that C-12-053 did not include the 16 hour duration efficacy evaluation visit and had an additional active comparator, PATANOL. Both studies evaluated the same efficacy endpoints (itching and redness) for the onset of action

and the 24 hours duration of action. The randomization ratio in C-10-126 was 1:1:1 and in C-12-053, it was 2:2:2:1 for PAZEO 0.7%: PATADAY: PATANOL: Vehicle.

Both studies were conducted in patients at least 18 years of age with a history of seasonal and/or perennial allergic conjunctivitis for at least 1 year prior to study entry and a positive allergic skin test within 24 months prior to study entry. Study C-12-053 had PATADAY, PATANOL and vehicle as comparators; however, PATANOL was dosed only once daily (instead of the approved twice-a-day regimen) at Visit 3A (the day before the 24-hour duration-of-action efficacy evaluation) and Visit 4.

The primary efficacy variable for both studies was patient-evaluated ocular itching severity scores (assessed using a 0-4 scale with 0.5 unit increments: 0 = none, 4 = incapacitating itch). In Study C-10-126, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visits 4B (16-hour duration-of-action) and 5 (onset-of-action). In Study C-12-053, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visit 3B (24-hour duration-of-action) and Visit 4 (onset-of-action).

In past CAC Studies, differences of approximately 1 unit between test product and vehicle observed in the majority of time points (two out of three in the case of these studies) has been considered clinically significant.

Secondary efficacy objectives included: to demonstrate superiority of PAZEO over vehicle and PATADAY at the 24-hour duration-of-action timepoint and to demonstrate superiority to vehicle for conjunctival redness associated with allergic conjunctivitis.

The majority of patients completed the two CAC studies as well as the Phase 3 safety study, C-12-028.

Study	**PAZEO (N)**		**Vehicle Control (N)**	
	Randomized	Completed (%)	Randomized	Completed (%)
C-10-126	66	63	68	60
C-12-053	98	93	49	48
C-12-028	331	329	169	166
TOTAL	495	485 (98%)	286	274 (96%)

Results for Ocular Itching

Efficacy results for ocular itching are shown in the table below:

In both studies, PAZEO was significantly better (p-value<0.0001) compared to vehicle for treating ocular itching associated with allergic conjunctivitis at onset-of-action, and 24-hour duration-of-action.

In Study C-10-126, at 24-hour duration-of-action, PAZEO was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. In Study C-12-053, PAZEO was superior to PATADAY for ocular itching associated with allergic conjunctivitis at 24-hour duration-of-action at 2 (3 and 5 minutes) out of 3 post CAC time points. The point estimate for the

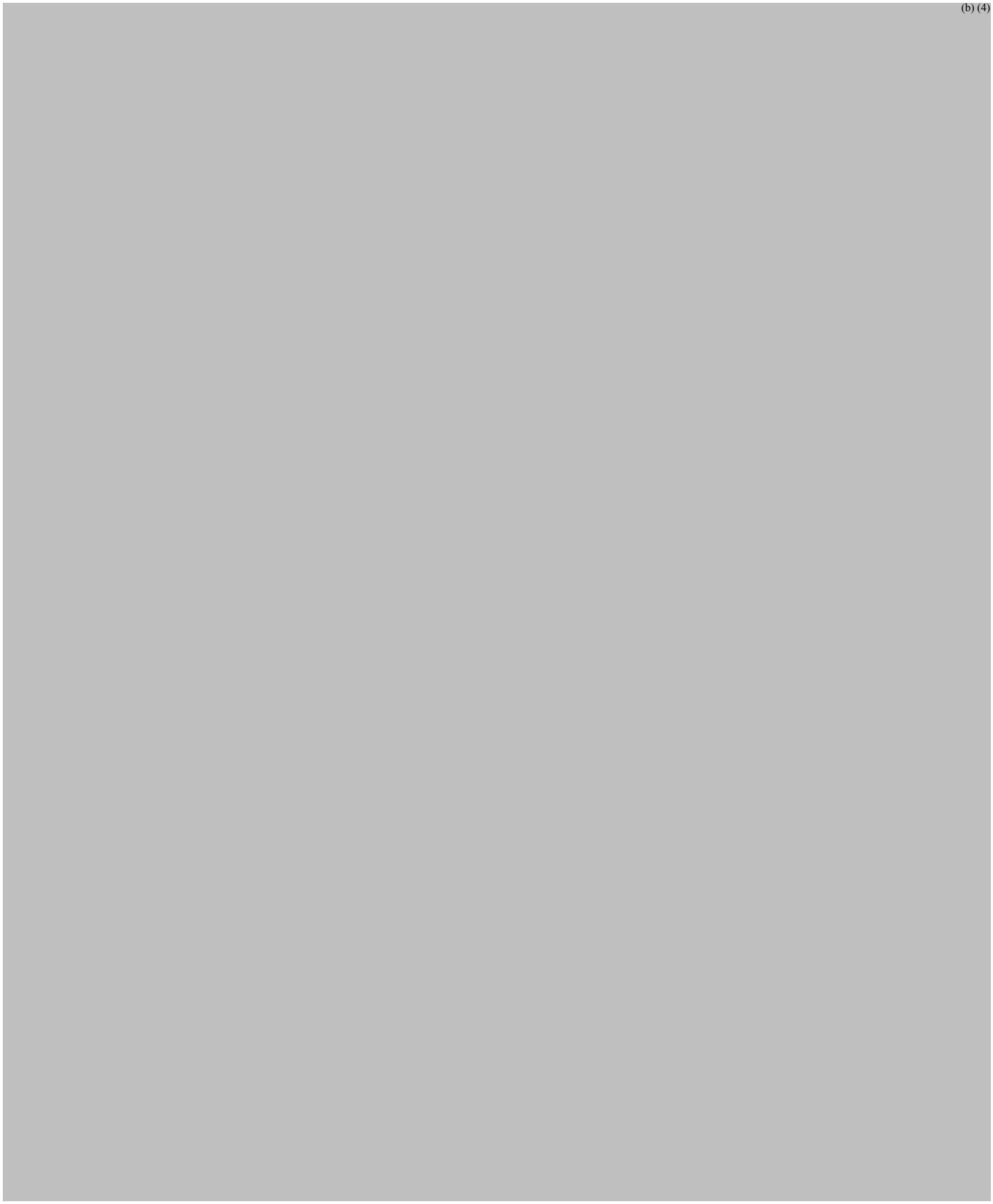
treatment difference at 7 minutes post-CAC was in favor of PAZEO but did not demonstrate statistical significance.

Itching Scores by Treatment Group and Treatment Difference* in Mean Itching

	Time Point	Olopatadine, 0.77%	PATADAY* (Olopatadine, 0.2%)		Vehicle	
STUDY C-10-126		(N = 66)	(N = 68)		(N = 68)	
		Mean	Mean	Difference (95% CI)	Mean	Difference (95% CI)
Onset	**Average**	0.46	0.54	-0.08 (-0.37, 0.21)	1.98	-1.51 (-1.81, -1.23)
	3 mins	0.36	0.39	-0.02 (-0.31, 0.26)	1.90	-1.54 (-1.82, -1.25)
	5 mins	0.53	0.61	-0.08 (-0.39, 0.22)	2.06	-1.53 (-1.84, -1.22)
	7 mins	0.48	0.61	-0.13 (-0.44, 0.17)	1.97	-1.49 (-1.80, -1.18)
16h	**Average**	0.75	0.96	-0.21 (-0.49, 0.07)	2.20	-1.45 (-1.73, -1.17)
	3 mins	0.70	0.87	-0.17 (-0.44, 0.11)	2.20	-1.50 (-1.77, -1.23)
	5 mins	0.79	1.04	-0.24 (-0.55, 0.07)	2.27	-1.48 (-1.79, -1.16)
	7 mins	0.75	0.98	-0.23 (-0.54, 0.08)	2.13	-1.38 (-1.69, -1.07)
24h	**Average**	1.04	1.48	-0.44 (-0.72, -0.16)	2.55	-1.51 (-1.79, -1.24)
	3 mins	0.93	1.41	-0.48 (-0.76, -0.20)	2.54	-1.61 (-1.88, -1.33)
	5 mins	1.10	1.52	-0.42 (-0.72, -0.12)	2.62	-1.51 (-1.81, -1.21)
	7 mins	1.09	1.50	-0.41 (-0.72, -0.10)	2.50	-1.41 (-1.72, -1.11)
Study C-12-053		(N = 98)	(N = 99)		(N = 49)	
Onset	**Average**	0.52	0.56	-0.05 (-0.24, 0.14)	1.91	-1.39 (-1.62, -1.16)
	3 mins	0.38	0.47	-0.09 (-0.28, 0.09)	1.91	-1.53 (-1.76, -1.30)
	5 mins	0.53	0.61	-0.08 (-0.29, 0.12)	1.99	-1.46 (-1.71, -1.22)
	7 mins	0.65	0.61	0.04 (-0.18, 0.26)	1.82	-1.17 (-1.45, -0.90)
24h	**Average**	1.16	1.40	-0.24 (-0.48, -0.00)	2.27	-1.11 (-1.40, -0.82)
	3 mins	1.01	1.33	-0.31 (-0.57, -0.06)	2.30	-1.29 (-1.60, -0.97)
	5 mins	1.22	1.48	-0.26 (-0.51, -0.01)	2.37	-1.15 (-1.46, -0.84)
	7 mins	1.25	1.41	-0.16 (-0.42, 0.11)	2.14	-0.89 (-1.22, -0.57)

** Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.;*
The ocular itching score range is 0-4, where 0 is none and 4 is incapacitating itch.

(b) (4)



8. Safety

See the clinical and statistical reviews.

The reviewers summarize that safety information for this application is primarily derived from Study C-12-028, a 6 week, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. Subjects at risk for developing allergic conjunctivitis, at least 2 years of age or older with asymptomatic eyes at the time of study entry were randomized in a 2:1 ratio to PAZEO or vehicle, respectively. Subjects younger than 6 years of age were randomized from one randomization schedule; subjects 6 years of age or older were randomized from another randomization schedule.

All randomized subjects received 1 drop of either PAZEO or vehicle in both eyes for 6 weeks. Safety variables and assessments included best-corrected visual acuity, slit-lamp, intraocular pressure (IOP), dilated fundus evaluations, pulse, blood pressure, and adverse events.

At the Baseline Visit (Day 0) and at each subsequent office visit (Week 1, Week 3, Week 6), best-corrected visual acuity was measured and slit-lamp evaluations were performed for the eyelids, conjunctiva, cornea, iris/anterior chamber, and lens. At the Baseline Visit (Day 0) and at the last office visit (Week 6), IOP was measured, a dilated fundus examination (DFE) of the vitreous, retina/macula/choroid, and optic nerve was performed, and vital signs (pulse and blood pressure) were taken. At each office visit and during telephone contacts at Weeks 2, 4, and 5, adverse events and dosing compliance were recorded and concomitant medications updated. The Exit Visit occurred via telephone contact at Week 7. Adverse events were recorded and concomitant medications updated.

The following safety information was obtained from the study:

- There were no deaths or serious adverse reactions reported.
- Two subjects entered with negative pregnancy test and became pregnant despite use of spermicide with barrier. Both delivered babies without congenital anomalies after the study.
- Fifty one pediatric patients between ages 2 through 16 years of age (median 5 years) were enrolled.
- There were no clinically significant changes noted in Visual Acuity, Intraocular Pressure, Slit Lamp or fundus exam in the studies. There were no significant differences in vital signs.
- Adverse events were comparable in the two arms

Study 12-028	**PAZEO**		**Vehicle**	
Adverse Events	**N=330**		**N=169**	
Deaths	0		0	
Discontinue due to Adverse Event	0		2	1.2%
Vision blurred	16	4.8%	7	4.1%

Dry eye	11	3.3%	5	3%
Corneal Staining	8	2.4%	7	4.1%
Dysgeusia	8	2.4%	0	
Abnormal sensation in eye	7	2.1%	7	4.1%
Nasopharyngitis	6	1.8%	3	1.8%
Upper respiratory tract infection	6	1.8%	3	1.8%
Conjunctival staining	6	1.8%	1	0.6%
Eye pruritus	5	1.5%	2	1.2%
Headache	5	1.5%	3	1.8%
Eye irritation	1	0.3%	5	3%
Ligament sprain	1	0.3%	2	1.2%
Cough	1	0.3%	2	1.2%
Conjunctival hemorrhage	0		2	1.2%
Diarrhea	0		2	1.2%
Gastroenteritis viral	0		2	1.2%

Reviewer Comment:
I agree there are no safety issues to preclude approval.

9. Advisory Committee Meeting

There were no efficacy and safety issues raised by this application to bring before the Advisory Committee. Olopatadine is not a new molecular entity.

10. Pediatrics

The application was presented before the Pediatric Review Committee (PeRC) on November 12, 2014. PeRC concurred with the applicant's request for a partial waiver for children less than two years of age because necessary studies are impossible or highly impractical, e.g., because the number of patients in that age group is so small or geographically dispersed.

Pediatric exclusivity was granted on December 16, 2014, based on the Pediatric Exclusivity Board's determination that the information submitted met the terms of the Pediatric Written Request.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

Overall the Office of Compliance found that facilities are acceptable as noted in the CMC review.

11.2 Office of Scientific Investigation (OSI) Audits

Two investigators were inspected and classified as NAI. OSI concluded the data generated by these clinical sites appear adequate in support of the indication.

11.3 Financial Disclosure

The financial disclosure information was reviewed by the Medical Officer, who notes the one investigator with an interest enrolled a small percentage of patients and is unlikely to impact the integrity of the data. In addition, the trials were double-masked, drug administration was given by staff personnel in the efficacy studies, and efficacy and safety variable were assessed by masked observers, and monitored for protocol compliance, all measures designed to mitigate bias.

12. Labeling

The package insert and carton and container labels were reviewed as applicable by DTOP, DMEPA, and OPDP/DPDP.

- **Package insert (PI):** The PI is written in PLR format.
- **Carton and Container Labels**: The labels have been reviewed by DTOP, OPQ and DMEPA. The carton/container labels have been finalized.
- **Proprietary Name**: The proprietary name PAZEO was found acceptable by DMEPA.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

NDA 206276 will be approved. All disciplines recommend approval of the application.

13.2 Risk Benefit Assessment

Allergic conjunctivitis occurs when the conjunctiva becomes swollen or inflamed due to a reaction to various allergens: pollen, dander, mold, or other allergy-causing substances. Normally the conjunctiva is a clear layer of tissue lining the eyelids and covering the white of the eye. However, the allergens cause release of histamine from mast cells, leading to hyperemia (redness) due to swelling of blood vessels and the eyes become itchy, red, puffy and teary. The condition may be exacerbated on hot, dry and windy days. Rain reduces the pollen burden.[1]

The mast cell's degranulation releases various preformed and newly formed mediators of the inflammatory cascade. Complications are very rare. Although allergic conjunctivitis may commonly reoccur, it rarely causes any visual loss. [2]

[1] Allergic Conjunctivitis http://www.nlm.nih.gov/medlineplus/ency/article/001031.htm
[2] ibid

There are a number of products, including H1 histamine receptor antagonists, mast cell stabilizers, an NSAID and a corticosteroid approved for the treatment of itching in the setting of conjunctivitis, or allergic conjunctivitis (redness and itching).

In the current NDA, the CAC study design and ocular itching and redness endpoints were used; these are the same design and endpoints as used in previous applications seeking the indication. Efficacy was for ocular itching but not redness demonstrated in two Phase 3 CAC studies, and safety was demonstrated in over 300 patients enrolled in a six-week study. The rate and scope of adverse reactions was low, and treatment did not adversely affect visual acuity or intraocular pressure, there were no drug-associated abnormalities identified on fundus exam, and vital signs were not affected.

The information in this application supports the safety and efficacy of PAZEO in the treatment of ocular itching in association with allergic conjunctivitis. The application will be approved.

13.3 Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)

None

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/s/

RENATA ALBRECHT
01/30/2015